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Date of Deposit July 19, 1996
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Ellen J. Kapinos

GI 5182ADIV

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants Hewick et al

Serial No. 08/319,831

Examiner: H. Kim

Filed October 6, 1994

Art Unit: 18

For BONE AND CARTIAGE INDUCTIVE PROTEINS

Honorable Commissioner of Patents
and Trademarks

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STATEMENT PURSUANT TO 37 CFR §1.825(a) and (b)

This is in response to the notice dated June 20, 1996, received from the Patent and Trademark Office indicating that the "Sequence Listing" does not comply with the requirements of §§1.821 through 1.825. To comply with the sequence rules, an amended Sequence Listing is submitted herewith.

Please substitute this amended Sequence Listing for the originally-filed Sequence Listing. The Sequence Listing and enclosed diskette contain amendments to correct defects identified in the Notice dated June 20, 1996.

Pursuant to the requirements of 37 CFR §1.821, *et seq.*, the undersigned attorney for Applicant(s) hereby state(s) to the best of his/her/their knowledge and belief, the content of the

Sequence Listing provided herewith and the computer readable copy of said Sequence Listing provided herewith are the same. These amendments present no substantive changes to the Sequence Listing as originally filed. No new matter has been added.

Respectfully submitted,



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LEGAL AFFAIRS
Genetics Institute, Inc.
87 CambridgePark Drive
Cambridge, MA 02140



41

SEQUENCE LISTING

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(1) GENERAL INFORMATION:

(i) APPLICANT: Hewick, Rodney M.
Wang, Jack H.
Wozney, John M.
Celeste, Anthony J.

(ii) TITLE OF INVENTION: Bone and Cartilage Inductive Proteins

(iii) NUMBER OF SEQUENCES: 15

(iv) CORRESPONDENCE ADDRESS:

(A) ADDRESSEE: Legal Affairs, Genetics Institute, Inc.
(B) STREET: 87 CambridgePark Drive
(C) CITY: Cambridge
(D) STATE: MA
(E) COUNTRY: USA
(F) ZIP: 02140

(v) COMPUTER READABLE FORM:

(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version #1.25

(vi) CURRENT APPLICATION DATA:

(A) APPLICATION NUMBER: US 08/319,831
(B) FILING DATE: 6-OCT-1994
(C) CLASSIFICATION:

(viii) ATTORNEY/AGENT INFORMATION:

(A) NAME: Kapinos, Ellen J.
(B) REGISTRATION NUMBER: 32,245
(C) REFERENCE/DOCKET NUMBER: GI 5182A-DIV

(ix) TELECOMMUNICATION INFORMATION:

(A) TELEPHONE: 617-876-1170
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(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 23 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:

(F) TISSUE TYPE: Bone

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

Arg His Glu Leu Tyr Val Ser Phe Gln Asp Leu Gly Trp Leu Asp Trp
1 5 10 15

Val Ile Ala Pro Gln Gly Tyr
20

(2) INFORMATION FOR SEQ ID NO:2:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 18 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

- (vi) ORIGINAL SOURCE:
 (A) ORGANISM: Bos taurus
 (F) TISSUE TYPE: Bone

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

Leu Ser Ala Thr Ser Val Leu Tyr Tyr Asp Ser Ser Asn Asn Val Ile
 1 5 10 15

Leu Arg

(2) INFORMATION FOR SEQ ID NO:3:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 7 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

- (vi) ORIGINAL SOURCE:
 (A) ORGANISM: Bos taurus
 (F) TISSUE TYPE: Bone

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

Ala Cys Cys Ala Pro Thr Lys
 1 5

(2) INFORMATION FOR SEQ ID NO:4:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 23 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:

(A) ORGANISM: Bos taurus

(F) TISSUE TYPE: Bone

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

Thr Asn Glu Leu Pro Pro Pro Asn Lys Leu Pro Gly Ile Phe Asp Asp
 1 5 10 15
 Val His Gly Ser His Gly Arg
 20

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 80 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: double

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:

(A) ORGANISM: Bos taurus

(vii) IMMEDIATE SOURCE:

(B) CLONE: acc30

(viii) POSITION IN GENOME:

(C) UNITS: bp

(ix) FEATURE:

(A) NAME/KEY: CDS

(B) LOCATION: 25..57

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

GGATCCGCGT GCTGTGCTCC GACC AAG CTG AGC GCC ACC TCC GTG CTC TAC 51
 Lys Leu Ser Ala Thr Ser Val Leu Tyr
 1 5
 TAC GAC AGCAGCAACA ATGTAATTCT AGA 80
 Tyr Asp
 10

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 11 amino acids

(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

Lys Leu Ser Ala Thr Ser Val Leu Tyr Tyr Asp
1 5 10

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 199 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(A) ORGANISM: Bos taurus

(vii) IMMEDIATE SOURCE:
(A) LIBRARY: Bovine genomic
(B) CLONE: Lambda 9800-10

(viii) POSITION IN GENOME:
(C) UNITS: bp

(ix) FEATURE:
(A) NAME/KEY: exon
(B) LOCATION: 30..199

(ix) FEATURE:
(A) NAME/KEY: intron
(B) LOCATION: 1..29

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 30..179

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

TGCCCCGCTGC CCCCTCCCGC CCCC GCCAG GTG CAC CTG CTG AAG CCG CAC GCG	53
Val His Leu Leu Lys Pro His Ala	
1 5	
GTC CCC AAG GCG TGC TGC GCG CCC ACC AAG CTG AGC GCC ACT TCC GTG	101
Val Pro Lys Ala Cys Cys Ala Pro Thr Lys Leu Ser Ala Thr Ser Val	
10 15 20	
CTC TAC TAC GAC AGC AGC AAC AAC GTC ATC CTG CGC AAG CAC CGC AAC	149
Leu Tyr Tyr Asp Ser Ser Asn Asn Val Ile Leu Arg Lys His Arg Asn	
25 30 35 40	
ATG GTG GTC CGC GCC TGC GGC TGC CAC TGAGGCCCCA ACTCCACCGG	196
Met Val Val Arg Ala Cys Gly Cys His	
45 50	

CAG

199

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 49 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

Val His Leu Leu Lys Pro His Ala Val Pro Lys Ala Cys Cys Ala Pro
 1 5 10 15
 Thr Lys Leu Ser Ala Thr Ser Val Leu Tyr Tyr Asp Ser Ser Asn Asn
 20 25 30
 Val Ile Leu Arg Lys His Arg Asn Met Val Val Arg Ala Cys Gly Cys
 35 40 45
 His

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 172 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:

- (A) ORGANISM: Bos taurus

(vii) IMMEDIATE SOURCE:

- (A) LIBRARY: Bovine genomic
- (B) CLONE: Lambda 9800-10

(viii) POSITION IN GENOME:

- (C) UNITS: bp

(ix) FEATURE:

- (A) NAME/KEY: exon
- (B) LOCATION: 51..161

(ix) FEATURE:

- (A) NAME/KEY: intron
- (B) LOCATION: 1..50

(ix) FEATURE:

- (A) NAME/KEY: intron
- (B) LOCATION: 162..172

(ix) FEATURE:

GGGGTGGGAG	GGCACGTGGA	TGGGACTCAC	CTTCTCCCAC	TACCCCCCAG	GAC TGG		56
					Asp Trp		
					1		
GTC ATC GCC CCC CAA GGC TAC TCA GCC TAT TAC TGT GAA GGG GAG TGC							104
Val Ile Ala Pro Gln Gly Tyr Ser Ala Tyr Tyr Cys Glu Gly Glu Cys							
		5			10		
						15	
TCC TTC CCG CTG GAC TCC TGC ATG AAC GCC ACC AAC CAC GCC ATC CTG							152
Ser Phe Pro Leu Asp Ser Cys Met Asn Ala Thr Asn His Ala Ile Leu							
	20				25		
						30	
CAG TCC CTG GTCAGTACCT C							172
Gln Ser Leu							
	35						

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 37 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

Asp Trp Val Ile Ala Pro Gln Gly Tyr Ser Ala Tyr Tyr Cys Glu Gly
1 5 10 15
Glu Cys Ser Phe Pro Leu Asp Ser Cys Met Asn Ala Thr Asn His Ala
20 25 30
Ile Leu Gln Ser Leu
35

(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 119 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: double
 (D) TOPOLOGY: linear

(vii) IMMEDIATE SOURCE:
 (A) LIBRARY: Bovine genous
 (B) CLONE: Lambda 9800-10

(viii) POSITION IN GENOME:

(C) UNITS: bp

(ix) FEATURE:

(A) NAME/KEY: exon

(B) LOCATION: 20..99

(ix) FEATURE:

(A) NAME/KEY: intron

(B) LOCATION: 1..19

(ix) FEATURE:

(A) NAME/KEY: intron

(B) LOCATION: 100..119

(ix) FEATURE:

(A) NAME/KEY: CDS

(B) LOCATION: 22..99

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

CCCTTGC GTG TCCCCG CAGA C GAC GTC CAC GGC TCC CAC GGC CGG CAG GTG 51
 Asp Val His Gly Ser His Gly Arg Gln Val
 1 5 10

TGC CGT CGG CAC GAG CTG TAC GTG AGC TTC CAG GAC CTG GGC TGG CTG 99
 Cys Arg Arg His Glu Leu Tyr Val Ser Phe Gln Asp Leu Gly Trp Leu
 15 20 25

GTGAGTTC CG ACTCTCCTTT 119

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 26 amino acids

(B) TYPE: amino acid

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

Asp Val His Gly Ser His Gly Arg Gln Val Cys Arg Arg His Glu Leu
 1 5 10 15

Tyr Val Ser Phe Gln Asp Leu Gly Trp Leu
 20 25

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1003 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: double

(D) TOPOLOGY: circular

(ii) MOLECULE TYPE: cDNA to mRNA

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:

(A) ORGANISM: Homo sapiens
(F) TISSUE TYPE: Human Heart

(vii) IMMEDIATE SOURCE:

(A) LIBRARY: Human heart cDNA library stratagene catalog
#936208
(B) CLONE: hH38

(viii) POSITION IN GENOME:

(C) UNITS: bp

(ix) FEATURE:

(A) NAME/KEY: CDS
(B) LOCATION: 8..850

(ix) FEATURE:

(A) NAME/KEY: mat_peptide
(B) LOCATION: 427..843

(ix) FEATURE:

(A) NAME/KEY: mRNA
(B) LOCATION: 1..997

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

GAATTCC GAG CCC CAT TGG AAG GAG TTC CGC TTT GAC CTG ACC CAG ATC	49
Glu Pro His Trp Lys Glu Phe Arg Phe Asp Leu Thr Gln Ile	
-139 -135 -130	
CCG GCT GGG GAG GCG GTC ACA GCT GCG GAG TTC CGG ATT TAC AAG GTG	97
Pro Ala Gly Glu Ala Val Thr Ala Ala Glu Phe Arg Ile Tyr Lys Val	
-125 -120 -115 -110	
CCC AGC ATC CAC CTG CTC AAC AGG ACC CTC CAC GTC AGC ATG TTC CAG	145
Pro Ser Ile His Leu Leu Asn Arg Thr Leu His Val Ser Met Phe Gln	
-105 -100 -95	
GTG GTC CAG GAG CAG TCC AAC AGG GAG TCT GAC TTG TTC TTT TTG GAT	193
Val Val Gln Glu Gln Ser Asn Arg Glu Ser Asp Leu Phe Phe Leu Asp	
-90 -85 -80	
CTT CAG ACG CTC CGA GCT GGA GAC GAG GGC TGG CTG GTG CTG GAT GTC	241
Leu Gln Thr Leu Arg Ala Gly Asp Glu Gly Trp Leu Val Leu Asp Val	
-75 -70 -65	
ACA GCA GCC AGT GAC TGC TGG TTG CTG AAG CGT CAC AAG GAC CTG GGA	289
Thr Ala Ala Ser Asp Cys Trp Leu Leu Lys Arg His Lys Asp Leu Gly	
-60 -55 -50	
CTC CGC CTC TAT GTG GAG ACT GAG GAT GGG CAC AGC GTG GAT CCT GGC	337
Leu Arg Leu Tyr Val Glu Thr Glu Asp Gly His Ser Val Asp Pro Gly	
-45 -40 -35 -30	
CTG GCC GGC CTG CTG GGT CAA CGG GCC CCA CGC TCC CAA CAG CCT TTC	385
Leu Ala Gly Leu Leu Gly Gln Arg Ala Pro Arg Ser Gln Gln Pro Phe	
-25 -20 -15	

GTG GTC ACT TTC TTC AGG GCC AGT CCG AGT CCC ATC CGC ACC CCT CGG 433
 Val Val Thr Phe Phe Arg Ala Ser Pro Ser Pro Ile Arg Thr Pro Arg
 -10 -5 1

GCA GTG AGG CCA CTG AGG AGG AGG CAG CCG AAG AAA AGC AAC GAG CTG 481
 Ala Val Arg Pro Leu Arg Arg Arg Gln Pro Lys Lys Ser Asn Glu Leu
 5 10 15

CCG CAG GCC AAC CGA CTC CCA GGG ATC TTT GAT GAC GTC CAC GGC TCC 529
 Pro Gln Ala Asn Arg Leu Pro Gly Ile Phe Asp Asp Val His Gly Ser
 20 25 30 35

CAC GGC CGG CAG GTC TGC CGT CGG CAC GAG CTC TAC GTC AGC TTC CAG 577
 His Gly Arg Gln Val Cys Arg Arg His Glu Leu Tyr Val Ser Phe Gln
 40 45 50

GAC CTT GGC TGG CTG GAC TGG GTC ATC GCC CCC CAA GGC TAC TCA GCC 625
 Asp Leu Gly Trp Leu Asp Trp Val Ile Ala Pro Gln Gly Tyr Ser Ala
 55 60 65

TAT TAC TGT GAG GGG GAG TGC TCC TTC CCG CTG GAC TCC TGC ATG AAC 673
 Tyr Tyr Cys Glu Gly Glu Cys Ser Phe Pro Leu Asp Ser Cys Met Asn
 70 75 80

GCC ACC AAC CAC GCC ATC CTG CAG TCC CTG GTG CAC CTG ATG AAG CCA 721
 Ala Thr Asn His Ala Ile Leu Gln Ser Leu Val His Leu Met Lys Pro
 85 90 95

AAC GCA GTC CCC AAG GCG TGC TGT GCA CCC ACC AAG CTG AGC GCC ACC 769
 Asn Ala Val Pro Lys Ala Cys Cys Ala Pro Thr Lys Leu Ser Ala Thr
 100 105 110 115

TCT GTG CTC TAC TAT GAC AGC AGC AAC AAC GTC ATC CTG CGC AAG CAC 817
 Ser Val Leu Tyr Tyr Asp Ser Ser Asn Asn Val Ile Leu Arg Lys His
 120 125 130

CGC AAC ATG GTG GTC AAG GCC TGC GGC TGC CAC TGAGTCAGCC CGCCCAGCCC 870
 Arg Asn Met Val Val Lys Ala Cys Gly Cys His
 135 140

TACTGCAGCC ACCCTTCTCA TCTGGATCGG GCCCTGCAGA GGCAGAAAAC CCTTAAATGC 930

TGTCACAGCT CAAGCAGGAG TGTCAGGGGC CCTCACTCTC GGTGCCTACT TCCTGTCAGG 990

CTTCTGGGAA TTC 1003

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 281 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

Glu Pro His Trp Lys Glu Phe Arg Phe Asp Leu Thr Gln Ile Pro Ala
 -139 -135 -130 -125

Gly Glu Ala Val Thr Ala Ala Glu Phe Arg Ile Tyr Lys Val Pro Ser

-120 -115 -110
 Ile His Leu Leu Asn Arg Thr Leu His Val Ser Met Phe Gln Val Val
 -105 -100 -95
 Gln Glu Gln Ser Asn Arg Glu Ser Asp Leu Phe Phe Leu Asp Leu Gln
 -90 -85 -80
 Thr Leu Arg Ala Gly Asp Glu Gly Trp Leu Val Leu Asp Val Thr Ala
 -75 -70 -65 -60
 Ala Ser Asp Cys Trp Leu Leu Lys Arg His Lys Asp Leu Gly Leu Arg
 -55 -50 -45
 Leu Tyr Val Glu Thr Glu Asp Gly His Ser Val Asp Pro Gly Leu Ala
 -40 -35 -30
 Gly Leu Leu Gly Gln Arg Ala Pro Arg Ser Gln Gln Pro Phe Val Val
 -25 -20 -15
 Thr Phe Phe Arg Ala Ser Pro Ser Pro Ile Arg Thr Pro Arg Ala Val
 -10 -5 1 5
 Arg Pro Leu Arg Arg Arg Gln Pro Lys Lys Ser Asn Glu Leu Pro Gln
 10 15 20
 Ala Asn Arg Leu Pro Gly Ile Phe Asp Asp Val His Gly Ser His Gly
 25 30 35
 Arg Gln Val Cys Arg Arg His Glu Leu Tyr Val Ser Phe Gln Asp Leu
 40 45 50
 Gly Trp Leu Asp Trp Val Ile Ala Pro Gln Gly Tyr Ser Ala Tyr Tyr
 55 60 65
 Cys Glu Gly Glu Cys Ser Phe Pro Leu Asp Ser Cys Met Asn Ala Thr
 70 75 80 85
 Asn His Ala Ile Leu Gln Ser Leu Val His Leu Met Lys Pro Asn Ala
 90 95 100
 Val Pro Lys Ala Cys Cys Ala Pro Thr Lys Leu Ser Ala Thr Ser Val
 105 110 115
 Leu Tyr Tyr Asp Ser Ser Asn Asn Val Ile Leu Arg Lys His Arg Asn
 120 125 130
 Met Val Val Lys Ala Cys Gly Cys His
 135 140

(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 112 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

Asp Val His Gly Ser His Gly Arg Gln Val Cys Arg Arg His Glu Leu
 1 5 10 15
 Tyr Val Ser Phe Gln Asp Leu Gly Trp Leu Leu Leu Val Ile Ala Pro
 20 25 30
 Gln Gly Tyr Ser Ala Tyr Tyr Cys Glu Gly Glu Cys Ser Phe Pro Leu
 35 40 45
 Asp Ser Cys Met Asn Ala Thr Asn His Ala Ile Leu Gln Ser Leu Val
 50 55 60
 His Leu Leu Lys Pro His Ala Val Pro Lys Ala Cys Cys Ala Pro Thr
 65 70 75 80
 Lys Leu Ser Ala Thr Ser Val Leu Tyr Tyr Asp Ser Ser Asn Asn Val
 85 90 95
 Ile Leu Arg Lys His Arg Asn Met Val Val Arg Ala Cys Gly Cys His
 100 105 110